ORGANIC LETTERS

2008
Vol. 10, No. 5
717−720

Synthesis of Pyranicin and Its Inhibitory Action with Bovine Heart Mitochondrial Complex I

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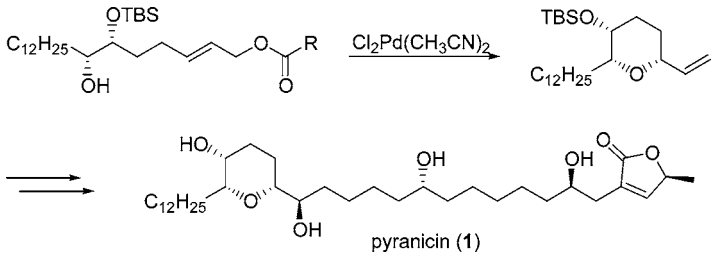
Received December 2, 2007

ABSTRACT



Total synthesis of pyranicin was achieved using $Cl_2Pd(CH_3CN)_2$-catalyzed diastereoselective cyclization of the allylic ester as the key step. The inhibitory activity of this compound for mitochondrial NADH–ubiquinone oxidoreductase (complex I) was slightly poorer than that of ordinary mono-THF acetogenins such as *cis*-solamin.

The annonaceous acetogenins, which are isolated from a number of tropical plants of *Annonaceae*, have attracted much attention in recent years due to a wide variety of biological features, including cytotoxic, antitumoral, and antimalarial activities. Their unique structures are characterized by a terminal α,β-unsaturated γ-lactone ring and a long aliphatic side chain which is connected with various oxygen-containing moieties such as THF, THP and/or epoxide rings, and several hydroxy groups on C-35 or C-37 carbon chain.

The inhibitory effect of acetogenins on mitochondrial NADH−ubiquinone oxidoreductase (complex I) is of particular importance since their diverse biological activities are thought to be attributable to this effect. Using systematically selected natural and synthetic THF-type acetogenins, Miyoshi and colleagues revealed that the alkyl spacer linking the γ-lactone and the hydroxylated THF moieties dynamically regulates the binding of these two toxophores to the putative binding sites.[1]

So far, over 430 acetogenins have been isolated from *Annonaceae*;[2−4] however, only eight contain a THP ring. Consequently, significant efforts have been devoted toward synthesis of THP-containing acetogenins due to their unique structures.[5] To our knowledge, the inhibitory action of THP-type acetogenins has not been characterized at the enzyme level.

Pyranicin (**1**) is a mono-THP acetogenin, first isolated from the stem bark of *Goniothalamus giganteus* in 1998 (Figure

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10.1021/ol702902w CCC: $40.75
Published on Web 02/06/2008

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1).[6] Pyranicin (**1**) has a C-13 alkyl spacer whose length is most suitable for the inhibition of complex I in the case of

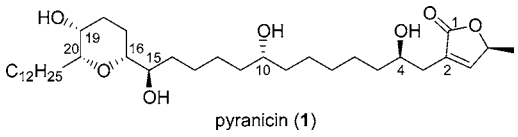


Figure 1. Structure of pyranicin.

mono- and bis-THF acetogenins.[1] Thus, it is very important to investigate the role of the THP ring in the inhibitory action.

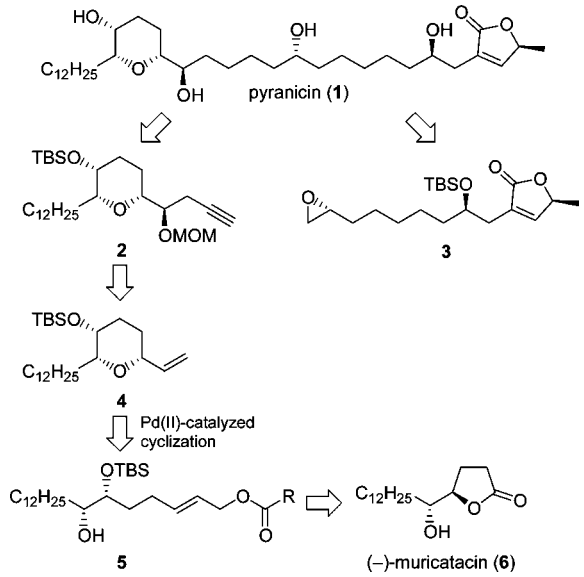
In 2003, Takahashi synthesized **1** via SmI_2-induced reductive cyclization of β-alkoxy acrilate.[5f] Strand also achieved synthesis of **1** using asymmetric Horner-Emmons reactions in 2005.[5c,d] Herein, we describe the total synthesis of **1** employing a Pd-catalyzed diastereoselective cyclization strategy.[7] This cyclization reaction would be attractive as a means to synthesizing other THP containing acetogenins.

Scheme 1 outlines our synthetic strategy. The key step is Pd-catalyzed diastereoselective cyclization. The starting material is (−)-muricatacin (**6**) which was reported by our group.[8]

As shown in Scheme 2, the key intermediate **5** was constructed as follows. Protection of **6** with ethyl vinyl ether and a catalytic amount of PPTS, followed by semireduction with DIBALH and careful Horner-Emmons reaction at −50 °C afforded α,β-unsaturated ester **7**. Protection of the hydroxy group of **7** with TBSCl and imidazole, and subsequent reduction with DIBALH gave allylic alcohol **8**. Esterification of **8** with various acid chlorides, followed by removal of the ethoxyethyl group with 0.5 N hydrochloric acid afforded the cyclization precursor **5** (Scheme 2).

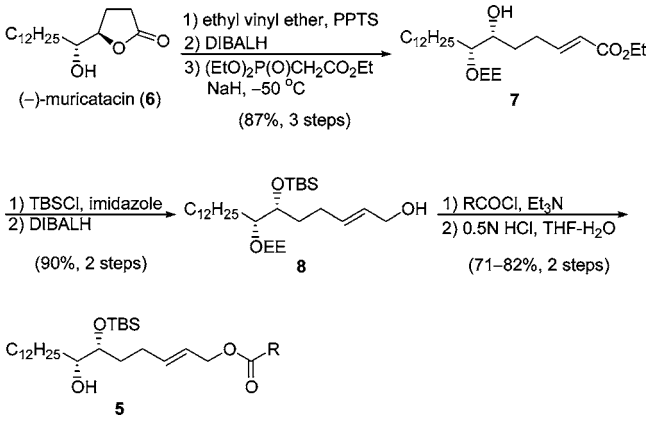
The results of diastereoselective cyclization of **5** are summarized in Table 1. While $Cl_2Pd(CH_3CN)_2$ was the most effective catalyst in the diastereoselective cyclization, $PdCl_2$ and $Cl_2Pd(PPh_3)_2$ were ineffective. As far as we have found, substituted aromatic esters such as biphenyl are appropriate

Scheme 1. Retrosynthetic Analysis



substrates. As for the solvent, CH_2Cl_2 gave a good selectivity although the yield was a little bit lower than that with DME.

Scheme 2. Preparation of Cyclization Precursor **5**



Determination of the relative stereochemistry of **4a** was performed by 2D-NOESY experiments of **4a′**, which was afforded by deprotection of the TBS group of **4a** with TBAF (Figure 2).

Diastereoselective dihydroxylation of **4a** by the Sharpless procedure using $(DHQD)_2AQN$ as a ligand gave **9** in 84% de.[9] The undesired diastereomer was removed by silica gel column chromatography.

Silylation of the hydroxy group of **9** with TBSCl, Et_3N, and DMAP, and subsequence treatment with tetrabutylammonium fluoride, furnished terminal epoxide **10**. Alkynylation of **10** with lithium acetylide, an ethylenediamine complex, followed by protection of the corresponding

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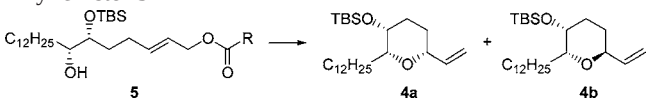
Table 1. Pd(II)-Catalyazed Diastereoselective Cyclization of Allylic Ester **5**



R	solvent	catalyst	time (h)	t (°C)	yield (**4a**+**4b**) (%)	**4a**:**4b**[a]
mesityl	DME	$Cl_2Pd(PPh_3)_2$	12	rt	–	–
mesityl	DME	$PdCl_2$	12	rt	49	78:22
mesityl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	73	84:16
mesityl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	78	67:33
t-Bu	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	23	81:19
phenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	29	83:17
biphenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	rt	99	90:10
biphenyl	DME	$Cl_2Pd(CH_3CN)_2$	12	0	N.R.	–
biphenyl	CH_2Cl_2	$Cl_2Pd(CH_3CN)_2$	4	−10	74	93:7

[a] The ratio of **4a** and **4b** was determined by ^{1}H NMR analysis.

hydroxy group with MOMBr and *i*-Pr_2NEt, afforded tetrahydropyran moiety **2** (Scheme 3).

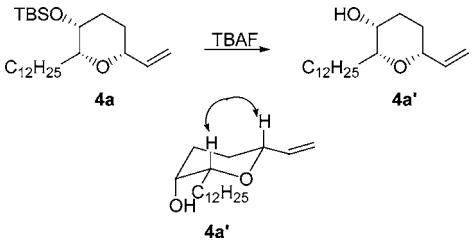
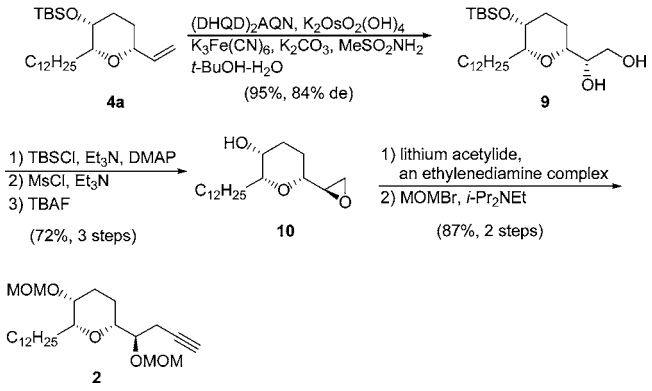


Figure 2. Determination of relative stereochemistry of **4a** using 2D-NOESY correlations.

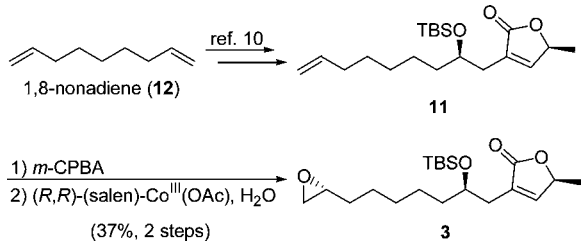
The γ-lactone moiety was prepared by Keinan's method[10] with Jacobsen's hydrolytic kinetic resolution.[11,12] Terminal

Scheme 3. Synthesis of THP Part



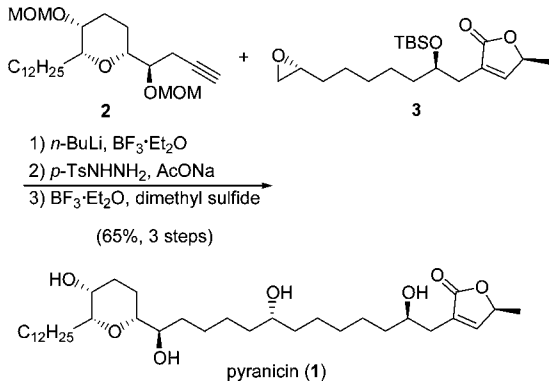
olefin **11** was constructed as we have reported earlier, starting from 1,8-nonadiene (**12**).[13] Olefin **11** was converted to epoxide using *m*-CPBA. Jacobsen's hydrolytic kinetic resolution gave γ-lactone moiety **3**, with an *R* configuration at the C-8 position (Scheme 4).

Scheme 4. Synthesis of γ-Lactone Part



Both segments **2** and **3** were coupled by the reported procedure at 75% yield,[14,15] followed by diimide reduction with *p*-$TsNHNH_2$ and sodium acetate in ethylene glycol diethyl ether.[16] Finally, deprotection of the TBS and MOM ether with $BF_3{\cdot}Et_2O$ afforded **1** (Scheme 5).

Scheme 5. Completion of Synthesis of Pyranicin



The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS spectra) of synthetic **1** were in good agreement with those of natural and synthetic pyranicin.[5c,d,f,6] The specific rotation value was consistent with that of synthetic **1** which was reported by Takahashi, who reported that natural and synthetic pyranicin were incompatible.[5f]

The inhibition of mitochondrial complex I was determined by NADH oxidase assay using bovine heart submitochondrial

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(15) The molecular ratio of oxyrane **3** to acetylene **2** was 1:5. With a ratio of 1:2, the corresponding product was afforded in 30% yield.
(16) Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973−977.

particles.[1b] The inhibitory potency (IC_{50} value) of *cis*-solamin, a natural acetogenin possessing a mono-THF ring, was 2.2 (±0.18) nM as a control.[17] Under the same experimental conditions, the IC_{50} of pyranicin was 7.5 (±0.30) nM, indicating that the inhibitory potency of this compound is slightly, but significantly, lower than that of *cis*-solamin. Considering the fact that the presence of multiple hydroxy groups in the spacer region is markedly adverse to the inhibition,[1a] the presence of an additional hydroxy group in the 10-position may be the cause of the decrease in the inhibitory potency of pyranicin. While the effect of the THP ring moiety may not be negligible, further systematic compound set is needed to confirm the effect of this moiety on the inhibition.

In conclusion, total synthesis of **1** was achieved from (−)-muricatacin (**7**) via Pd(II)-catalyzed diastereoselective cyclization. Pyranicin (**1**) was investigated in terms of its inhibitory action with bovine heart mitochondrial complex I. The inhibitory activity of this compound on complex I was slightly poorer than that of ordinary mono-THF acetogenins such as *cis*-solamin.

(17) Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651−10657.

Acknowledgment. This work was supported in part by a Grant-in-aid from the Japan Society for the Promotion of Science (90313840).

Supporting Information Available: Experimental procedures for compounds **1**−**5**, **7**−**10**, and **12**; ^1H and ^{13}C NMR spectra for **1**−**4a**; ^1H and 2D-NOESY spectra for compound **4a′**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702902W